REMARKS

Claims 1-22, 36 and 39-41 presently appear in this case. No claims have been allowed. The examiner states that claims 3, 11-17 and 19-22 have been withdrawn from consideration. It is assumed, however, that the examiner also intended to include claim 36 among those claims which have been withdrawn from consideration and thus it will be treated as such. The Official Action of January 27, 2009, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method of treating and/or preventing graft rejection in a subject in need thereof by administering a therapeutically effect amount of at least one copolymer 1 or copolymer 1-related heteropolymer in combination with at least one immunosuppressive drug.

The examiner states that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences but which are not included in a sequence listing. The examiner refers to the sequences on page 23 of the specification and has required that a new sequence listing be submitted that includes these sequences.

Attached hereto is a new sequence listing in the form of a .txt file. It is requested that this new sequence listing

be used as both the paper copy and the computer-readable form. Applicants have amended the specification at page 23 to identify the sequences therein as SEQ ID NOs:33-36, and the attached new sequence listing includes these sequences, as supported by the specification as filed.

The following statement is provided to meet the requirements of 37 C.F.R. §1.825(a) and 1.825(b).

I hereby state, in accordance with 37 C.F.R. §1.825(a), that the amendments included in the substitute sequence listing are believed to be supported in the application as filed and that the substitute sequence listing is not believed to include new matter.

I hereby further state, in accordance with 37 C.F.R. §1.825(b), that the.txt file submitted herewith constitutes both the computer readable form as well as the paper copy of the sequence listing, and therefore they are the same.

Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and

an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full

consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

As the examiner's requirement for a new sequence listing has now been fulfilled, reconsideration and withdrawal of this requirement is respectfully urged.

The examiner has objected to the specification because the priority information is not listed on page 1 thereof and correction has been required. This requirement is respectfully traversed.

The examiner's attention is invited to the Preliminary Amendment filed concurrently with the filing of the present application. In this Preliminary Amendment, a Cross-Reference to Related Applications was added after the title, which includes reference to the international application of which the present application is the national stage as well as reference to the provisional application whose benefit is claimed. It is noted that this Preliminary Amendment appears in the PAIR pages of the Patent and Trademark Office website, so it is clearly of record in this case. If it has not been formally entered, it is requested that it be formally entered and that the present objection be withdrawn.

Claims 1, 2, 4-10, 18 and 39-41 have been rejected under 35 U.S.C. §112, second paragraph, as failing to set forth the subject matter that applicant(s) regard as their invention. The examiner states that claim 1 is indefinite because the language is confusing where the claim recites "at least three amino acids each one selected from the at least three of the following groups:…"

Claim 1 has now been amended to clarify this language and to specify that the heteropolymer comprises "one amino acid selected from each of at least three of the following groups:…". This is identical to the language which appears in US Patent 6,844,314 (note claim 3). This language is no longer indefinite. Claims 8, 12 and 22 have also been amended to eliminate any indefiniteness in this regard. Reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1, 2, 4-10, 18 and 39-41 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Arnon in view of Shapiro. The examiner states that Arnon teaches inhibition of graft versus host disease and utilizes copolymer 1. The examiner recognizes that Arnon does not teach immunosuppressive drugs, but states that Shapiro discloses copolymer 1 and the use of the immunosuppressive drug cyclosporine at paragraphs 21, 298, 466 and 758 [the issued patent has no paragraph numbers, so applicant

cannot determine to which paragraphs the examiner refers; it is requested that the examiner refer to the paragraphs by column and line number]. Accordingly, the examiner considers it to have been obvious to combine copolymer 1 and cyclosporine in a method of immunosuppression of HVG because Arnon teaches the use of copolymer 1 in inhibiting GVH disease and Shapiro teach the immunosuppressive drug cyclosporine. Thus, one of ordinary skill in the art would have been motivated to combine the teachings of Arnon and Shapiro. This rejection is respectfully traversed.

Contrary to the examiner's statement, applicant can find nothing in Arnon which teaches inhibition of graft versus host disease. Arnon relates to the treatment of multiple sclerosis by ingestion or inhalation of copolymer 1. Applicant can find no disclosure in Arnon suggesting that their claimed method may be used for any other disease than multiple sclerosis. Since Arnon does not teach prevention of graft rejection, a person skilled in the art would not be motivated to combine its teaching with that of Shapiro.

Furthermore, Shapiro also teaches nothing about graft rejection or treatment of host versus graft responses. All the present claims are drawn to a method of treating or preventing graft rejection. Such claims cannot be made obvious by any combination of references, none of which are for treatment of

graft rejection. The treatment of multiple sclerosis is not the same as the treatment of graft rejection.

Furthermore, Shapiro does not make it obvious to combine copolymer 1 with cyclosporine for any reason as Shapiro does not teach the combination of copolymer 1 and cyclosporine A. Shapiro states at column 44, Example 6, lines 40-44:

> Clinical treatment of multiple sclerosis may be improved by use of the invention originally disclosed in U.S. patent application 07/660,561 [disclosing the use of carbonyl trapping agents] in combination with known medicaments including co-agent use of:...

The publication then lists various medicaments including (line 47) "(b) copolymer-1" and (line 53) "(c) cyclosporine..."

Contrary to the examiner's allegation, Shapiro does not disclose or suggest the combined use of copolymer 1 and cyclosporine. Rather, the cited publication mentions copolymer 1 and cyclosporine as two separate medications that may be used with carbonyl trapping agents to clinically treat multiple sclerosis.

While the examiner has not established a *prima facie* case of obviousness for the reasons discussed above, even if the examiner had established a *prima facie* case of obviousness, the evidence of unexpected results throughout the present specification would rebut such a rejection. Note page 3, lines

27-30, of the present specification, which states that the invention is based on the discovery that copolymer 1 in combination with at least one additional immunosuppressive drug "exhibit an unexpected synergistic effect for the treatment or prevention of HVG." See also the following sentence which states, particularly at page 4, line 1, that the combination induces an unexpected synergistic effect and thus improves the efficacy of the current immunosuppressive regimens. Page 4, lines 14-17, also states that the combination induces "a synergistic effect and thus enable the reduction in the dosage and toxicity of the current immunosuppressive regimens." Similarly, the sentence at page 17, lines 15-18, is to the same effect. See also page 17, lines 23-25. See also the discussion of Table 6 in Example 4, beginning at page 30, line 18, which specifically discusses the unexpected and synergistic results obtained in that experiment.

Despite the disclosure throughout the present specification that the present invention is based on synergistic results, the examiner has disregarded this disclosure and the supporting experimentation and has only discussed an alleged *prima facie* case of obviousness. Though applicant disagrees that a *prima facie* case of obviousness has been established, even if one had been established, the disclosure of unexpected results in

the present specification should be sufficient to rebut it. For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /rlb/
Roger L. Browdy
Registration No. 25,618

RLB:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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